REMARKS

This Amendment and Remarks are filed in response to the Office Action dated August 7, 2007, wherein all pending claims stand rejected. The Response is accompanied by a Request for Continuing Examination (RCE).

Previously pending claims in the application were 4-9, 13-17 and 23, 24, 27, 30-33 and 35-37. With this amendment, claims 1-37 are canceled. New claims 38-48 are added.

Objections to Claim 30

Claim 30 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 24. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Applicants believe that Examiner meant Claim 23.

Applicants disagree and maintain that there were sufficient differences between claims 23 and 30. However, in the interest of advancing the examination, Applicants canceled all previously pending claims and submit herewith a new set of claims 38-48.

The newly submitted claims obviate the objection to claim 30.

Claim Rejections under 35 USC § 112, First Paragraph

Claims 4-9, 13-17, 23, 24, 27, 30-33 and 35-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Specifically, Examiner maintains that support is not found in

the specification for methods as required by claims 23 and 30 and that the specification fails to describe expanding and suspending as required by step b) of the claims.

Applicants disagree. However, in the interest of advancing the prosecution, Applicants canceled previously pending claims and submit herewith a new set of claims 38-48 that take in consideration all previous Examiner's rejections. The new independent claim 38 comprises steps (a) through (h). Support for these steps is found as indicated below:

a) isolating autologous or heterologous chondrocytes (page 50, lines 12-13; page 22, lines 34-36) or providing cells that could be differentiated into chondrocytes (page 49, lines 28-32);

b) expanding (page 24, lines 11-27) said chondrocytes or cells in a growth medium (page 24, line 14);

c) suspending (page 24, lines 30-32) said isolated expanded chondrocytes or cells in a collagen-containing solution(page 24, lines 31-33, page 25, lines 20 and 23-25);

d) providing a three-dimensional support matrix (page 50, line 3) containing plurality of pores (page 27, lines 32-36)

e)incorporating the suspension of step c) into said support matrix (page 25, lines 35-37), thereby producing a seeded matrix (page 24, lines 24-27);

f) preparing said construct for implantation into said cartilage lesion by activating said chondrocytes or cells by subjecting said seeded support matrix to condition promoting activation and propagation of chondrocytes (page 33, lines 13-24), wherein said conditions comprise perfusing said support matrix with a culture medium at a flow rate from about 1 μL/min to about 500 μL/min (page 49, lines 7-8) and applying a protocol consisting essentially of applying to said seeded support matrix hydrostatic

pressure from about 0.01 MPa to about 10 MPa (page 36, line 33) above atmospheric pressure (page 33, lines 30 and 31; page 36, line 31) at about 0.01 to about 1 Hz (page 49, line 12), wherein the time for applying the hydrostatic pressure is from about 1 to about 8 hours (page 77, line 23) followed by applying a static atmospheric pressure for from about 16 to about 23 hours (page 77, line 23 and 24) said protocol repeated for from about 1 hour to about 90 days (page 49, lines 16-18);

g) implanting said construct into said cartilage lesion (page 4, lines 29-30, page 59, lines 25-27); and

h) depositing polyethylene glycol cross-linked with methylated collagen (page 4, lines 31-32, page 68, lines 23-29) over said construct wherein said deposition of polyethylene glycol cross-linked with methylated collagen over said implanted construct results in formation of the superficial cartilage layer that overgrows said construct implanted within said lesion (page 67, lines 18-20 and page 68, lines 25-29).

Claim 39 is directed to an additional step i) wherein a bottom tissue sealant is deposited into said cartilage lesion before said construct is implanted therein

wherein said bottom sealant is selected from the group consisting of gelatin, a copolymer of polyethylene glycol and poly-lactide or poly-glycolide, periodate-oxidized gelatin, 4-armed pentaerythritol thiol and a polyethylene glycol diacrylate, 4-armed tetra-succinimidyl ester or tetra-thiol derivatized PEG, photo-polymerizable polyethylene glycol-co-poly(α-hydroxy acid) diacrylate macromer, 4-armed polyethylene glycol derivatized with succinimidyl ester and thiol further cross-linked with methylated collagen, derivatized polyethylene glycol (PEG), polyethylene glycol (PEG) cross-linked with alkylated collagen, tetra-

hydrosuccinimidyl or tetra-thiol derivatized PEG, PEG cross-linked with methylated collagen, and a combination thereof (pages 56-59, particularly page 58, lines 33-35 and page 59, lines 1-17).

Claim 40 is directed to a sponge, scaffold, honeycomb or honeycomb-like lattice support matrix prepared from a compound selected from the group consisting of a Type I collagen, Type II collagen, Type IV collagen, gelatin, agarose, cell-contracted collagen containing proteoglycans, glycosaminoglycans or glycoproteins Type I collagen (page 11, lines 23-35, page 27, line 37).

Claim 41 is directed to the support matrix prepared from Type I collagen (page 28, lines 28-30).

Claim 42 is directed to hydrostatic cyclic pressure applied from about 0.05 MPa to about 3 MPa at 0.1 to about 0.5 Hz (page 49, line 15).

Claim 43 is directed to a perfusion flow rate of from about 5 μL/min to about 50 μL/min (page 49, line 8).

Claim 44 is directed to a perfusion flow rate is about 5 μL/min (page 49, line 9).

Claim 45 is directed to cell activation performed under oxygen concentration from about 1% to about 20% (page 49, lines 9 and 10) and in claim 46 under oxygen concentration from about 2% to about 5% (page 49, line 10).

Claim 47 is directed to the superficial cartilage layer into or provides the same type of surface as a synovial membrane of the intact joint (page 68, lines 23-29, page 69, lines 21-30, Figures 10B, 12A-C).

Claim 48 is directed to the construct prepared *in vitro*, *ex vivo* or *in vivo* (page 77, Example 9).

With the all new claims being shown to be supported by the

specification, the rejections under 35 USC 112, first paragraph are overcome.

Applicants now turn to respond to Examiner's specific rejections.

Examiner claims that the specification also fails to describe using a plurality of conditions promoting activation and propagation that can each be used alone or in any combination as required in step d) of claims 23 and 30.

Applicants disagree. However, new claims and Remarks above clearly specify conditions under which the propagation and activation is achieved.

Examiner asserts that support is not found in the specification for a range of about 0.01 MPa to about 10 MPa for applying hydrostatic pressure, a range of "about 1 to about 8 hours" for applying hydrostatic pressure, and a range of "16 to about 23 hours per day for applying a static atmospheric pressure in claims 23 and 30.

Applicants disagree. All these conditions, as they now appear in new claim 38 are shown to be supported above in a concise form dealing with support for all steps of the new claims. As requested, the pages and lines of the specification where the ranges are recited are pointed out.

Support is further not found in the specification for step b) of claims 23 and 30, i.e. both expanding and suspending in collagen, collagen gel, collagen sol, or a collagen-containing solution.

Applicants disagree. Support for new claims is listed above.

Support is not found in the specification for collagen containing materials as recited in claim 4. The specification (paragraph bridging pages 11 and 12) discloses cell-contracted

collagen containing proteoglycans, glycosaminoglycans or glycoproteins. Support is not found for collagen other than cell-contracted collagen containing proteoglycans, glycosaminoglycans or glycoproteins.

Applicants disagree. However, to advance the prosecution, Applicants' new claims mirror the disclosure on page 11, lines 23, lines 26-35.

Additionally, the specification fails to support that materials other than proteoglycans, glycosaminoglycans or glycoproteins recited in the paragraph are to be contained by cell-contracted collagen.

Applicants disagree. New claims take Examiner's rejections into consideration and claim the subject matter as strictly disclosed in the specification.

Support is not found in the specification for a range of "about one to about 28 days" at an atmospheric pressure as in claim 14. The page and line where this range is recited should be pointed out.

Applicants disagree. Claim 14 is canceled.

Support is not found in the specification for superficial cartilage layer integrated into a synovial membrane as required by claim 27.

Applicants disagree. Such support is indicated for the new claim 47.

Support is not found in the specification for further limiting a method as required by claim 30 as required by claims 31-33 and 35-37.

Applicants disagree. Claims 30-37 are canceled.

It is respectfully submitted that the new claims are all supported in the specification and therefore, the rejection is

overcome.

Claim Rejections Under 35 USC § 112, Second Paragraph

Claims 4-9, 13-17, 23, 24, 27, 30-33 and 35-37 are rejected under 25 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 23 and 30 and other claims noted above not having support in the specification are confusing and unclear by claiming methods not described in the specification. Claiming several different procedures for activation for use each alone or in combination in step d) of the claims especially makes the claims unclear since the alternative procedures differ substantially such that selecting one procedure or a combinations of procedures will result in a substantially different method than when using another activation procedure or another combination of activation procedures. Furthermore, setting forth pressure and time period for hydrostatic pressure and static atmospheric pressure, flow rate and percent oxygen is confusing since hydrostatic pressure, static atmospheric pressure, flow rate and oxygen content are alternative to each other and to other activation procedures and do not have to be used for activation in step d). For example, activation can result from only temperature, length of time, cell density, carbon dioxide content, or any combination of these.

Applicants disagree, however, since Claims 23 and 30 are canceled, the rejection is moot.

Step b) of claims 23 and 30 are confusing by requiring expanding and suspending in the same step. Expanding and suspending are separate steps, and cannot be performed as the same time.

Furthermore, it is uncertain as to steps that constitute "expanding", and it is not seen how expanding and suspending can be

in collagen or a collagen gel since these are solid materials.

Applicants disagree. The new claims separate two steps. For Examiner's information, collagen gel is not a solid material and cell can be suspended therein, however, the new claims limit suspending step to a collagen-containing solution.

Claims 23 and 30 are further unclear by requiring cells that could be differentiated into chondrocytes in step a) since all of the subsequent steps relate only to chondrocytes.

Applicants disagree, however, the new claims claim chondrocytes and cells.

Requiring constant hydrostatic pressure to have an Hz range is confusing since it is not seen how constant pressure can change to have an Hz range.

Applicants disagree, however, in the instant claims the constant pressure is not claimed.

Claim 24 in line 5 is confusing by reciting "may be" since such language does not require the sealant to be that recited. Additionally, ---bottom adhesive --- should be recited before "sealant" in line 5 of the claim to be clear that the sealant is the bottom adhesive sealant.

Applicants disagree. Claim 24 is canceled.

Claim 30 in step f) is unclear by not having clear antecedent basis for "the neo-cartilage". Additionally, in step g) there is not clear antecedent basis for "the polyethylene glycol cross-linked with methylated collagen".

Applicants disagree, however, claim 30 is canceled and the rejection is moot.

Claims 31 and 32 are unclear by requiring the top or bottom sealant to be selected from a group of materials since claim 30 limits the top sealant to polyethylene glycol cross-linked with

methylated collagen. In claim 30 the top sealant cannot be a material other than polyethylene glycol cross-linked with methylated collagen, and a dependent claim that encompasses the top sealant being another material is improper.

Applicants disagree, however, both claims are canceled. The new claims take into consideration Examiner's rejections.

Claim 35 is unclear by depending on canceled claim 34. There is not antecedent basis for "said perfusion flow rate" in line 2 of claim 35.

Applicants disagree. However, they canceled claim 35.

Claim 37 is unclear by not having antecedent basis for "said perfusion and pressure" in line 2. Claim 36 does not require both perfusion and pressure.

Applicants disagree, however, to advance the examination, Applicants canceled claims 35-37.

With these amendments, all rejections under 35 USC 112, second paragraph are overcome. the rejections should be withdrawn.

Claim Rejections - 35 USC § 103

Claims 4-6, 13-17, 23 and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al (6,528,052 B1) in view of Wise et al (American Surgeon) and Rhee et al (5,475,052), and if implanting a cartilage construct into the lesion, and covering the construct: with a layer of a top adhesive sealant that is polyethylene glycol (PEG) cross-linked with methylated collagen. In claim 23 the method is carrier out by isolating chondrocytes from cartilage, expanding and suspending the chondrocytes, seeding the chondrocytes suspension into a support matrix, preparing a construct for implantation by subjecting the seeded support to conditions that promote activation and propagation of the chondrocytes, implanting the construct in a cartilage lesion, and

depositing over the construct a top adhesive sealant that is PEG cross-linked with methylated collagen, which results in formation of a superficial cartilage layer over growing the implanted construct.

Smith et al disclose formation of cartilage tissue *in vitro* from chondrocytes and implanting the cartilage (col 9, lines 22-33). The cartilage is formed by isolating cartilage cells, and culturing the cells while in a scaffold or support (col 9, line 30). The resultant cartilage tissue is transferred to a defect (col 9, lines 35-40).

Wise et al disclose using a collagen-polyethylene glycol sealant to seal leaks after liver transplantation.

Rhee et al ('052) disclose using a collagen-polyethylene glycol matrix (cols 15-17 and col 20, line 60 to col 23, line 67) for implant applications.

Rhee et al ('519) disclose using a collagen-polyethylene g1ycol conjugate for ophthalmic applications (cols 9-20).

It would have been obvious to seal a defect after implanting cartilage tissue in a defect as disclosed by Smith et al using a collagen-polyethylene glycol sealant as suggested by Wise et al using this sealant and Rhee et al using a collagen-polyethylene glycol matrix for implant applications. It would have been obvious that sealing the defect after implanting will be advantageous to prevent contamination and infection at the site of the defect. The cartilage produced by Smith et al before implanting is inherently a construct.

If needed Rhee et al ('519) would have further suggested using a collagen-polyethylene glycol sealant from disclosing using a collagen-polyethylene glycol conjugate for ophthalmic applications. The activation procedures in claim 23 are alternative and do not

have be by using cyclic or constant hydrostatic pressure, static atmospheric pressure, flow rate or oxygen percent, and the specific conditions for these activation procedures are not required by claim 23. In any event, a hydrostatic pressure as in claim 23 is disclosed by Smith et al. Methylated collagen in claim 23 is taught by Rhee et al ('052) (col 16, line 29). The parent application does not antedate Wise et al since the presently claimed invention is not disclosed in the parent application.

Applicants disagree. While Smith discloses some of the steps in the method, the gist of this invention is the finding that by depositing a very specific sealant, namely polyethylene glycol cross-linked with methylated collagen, over implanted construct comprising activated chondrocytes or other cells, as claimed herein in step h) of claim 38, the implant in combination with the sealant results in overgrowing said defect with a superficial cartilage layer. The sealant deposition is NOT, as Examiner believes, placed there to insulate the implant from contamination and infection at the site of the defect. During development of this invention, it has been found that deposition of this particular sealant actually results in formation of a "superficial cartilage layer", an outermost layer of cartilage that forms the layer of squamous-like flattened superficial zone chondrocytes covering the layer of the second sealant and overgrowing the lesion (page 14, lines 14-17). Such formation does not appear when other sealants are used, and has never before been disclosed or described, not even in Smith reference.

As described on page 50 and following pages, in section III, "The primary aspect of this invention is a finding that when the neo-cartilage, neo-cartilage construct or seeded support matrix produced according to procedures and conditions described above is

implanted into a cartilage lesion cavity and covered with a biocompatible adhesive sealant, the resulting combination leads to a formation of a superficial cartilage layer completely overgrowing said lesion."

Examiner's attention is directed to Figures 10-12 and language in Spec., pages 62-64, describing results of the actual experimental implantation of the construct of the invention into the cartilage defect covered with the sealant according to the invention. Figures 10-12 clearly illustrate formation of the new layer of superficial cartilage cells.

The porcine implant site is seen in Figure 10B which also show initiation of formation of a superficial cartilage layer two weeks after implantation.

Comparison of Figure 11 (control at four months after arthrotomy) and Figure 12 shows test knee three month following arthrotomy and neo-cartilage construct implantation according to the invention. The Figure 11 (control) shows that in the control knee there is a visible formation of fibrocartilage, functionally deficient cartilage tissue. In the test group (Figures 12A-12D), the implanted porcine neo-cartilage construct resulted in production of dense regenerating hyaline cartilage and in the same test group, there was clearly visible cell integration (Figures 12C and 12D) and formation of the superficial cartilage layer (Figures 12A and 12B), see page 63, lines 24 and 25.

Figures 11A-11C show the control lesion at 4 months following the surgery without a treatment with the neo-cartilage construct. Noticeable in Figure 11A is the proliferation of undesirable fibrocartilage within the defect site. Also seen is synovial tissue that has infiltrated into the subchondral space, also an unwanted event.

Figures 12A-12D, experimental group treated with the implantable construct and covered with the PEG-methylated collagen adhesive, on the other hand, show that after 3 months post implantation in a weight bearing region of the knee, the neo-cartilage construct implant has produced dense hyaline-like cartilage and has integrated with the host cartilage laterally and at the interface of the subchondral bone.

Additionally, Figure 12A shows a formation of regenerated hyaline-like cartilage at the implant site; Figure 12B shows the beginning of integration between the porcine neo-cartilage and the native cartilage laterally and at the subchondral bone. Figure 12C shows already regenerated hyaline-like cartilage and Figure 12D shows chondrocytes integration into the surrounding native cartilage.

The construct was delivered to the defect by implantation of neo-cartilage construct between two layers of sealant. The newly formed superficial cartilage layer formed over the defect at three months following the implantation is clearly visible in Figure 12.

Figure 12 thus shows and confirms that 3 months after implantation in a weight-bearing region of the knee, the construct produced dense hyaline-like cartilage and has integrated within the host cartilage laterally and at the interface of the subchondral bone and was covered with a newly formed superficial cartilage layer.

It is respectfully submitted that no combination of references will result in the results as claimed, disclosed in the specification and supported with actual results obtained in experiments performed on mammalian subject.

Examiner is respectfully requested to reconsider his rejections and let the new claims pass to issue.

Double Patenting

Claims 4-9, 13-17, 23, 24, 27, 30-33 and 35-37 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6,528,052 B1 in view of Wise et al and Rhee et al (5,475,052), and if necessary in further view of Rhee et al (5,565,519).

For the type of reasons set forth above, it would have been obvious to seal a defect after implanting the in vitro formed cartilage of claim 16 of the patent using a sealant suggested by Wise et al and Rhee et al ('052), and if needed Rhee et al ('519). Formation of a superficial cartilage layer will be inherent when the defect containing the sealed implanted construct heals.

Applicants disagree. Applicants have shown above in the Remarks that the reference Smith does not disclose the whole invention. Smith's claims are directed to the method for repair of cartilage by submitting the cartilage, cartilage graft or chondrocytes to hydrostatic pressure. There is no artificial implant involving the support matrix involved, the cartilage used is the actual cartilage removed from the joint. Such cartilage is treated in vitro, in vivo or ex vivo. Formation of the newly formed superficial cartilage layer is nowhere disclosed and cannot be implied form the combination and definitely is not inherent, as Examiner argues, "when the defect containing the sealed implanted construct heals." Such formation of the new superficial layer was not observed when the other sealants were used or when the implant was used without the top sealant. The step of deposition the tissue adhesive over the implant is not disclosed for any of the implants used for cartilage repair and the combination of the construct with a sealant deposition resulting in formation in the newly formed superficial cartilage that is based on properties of one specific

tissue adhesive could not be foreseen until the actual clinical studies on animal were performed.

It is respectfully requested that Examiner reconsiders the Double Patenting obviousness rejection and withdraw the rejections.

SUMMARY

In summary, all previously pending claims are canceled and the new claim 38-48 are added. Arguments overcoming the rejections under 35 USC 112, first and second paragraph, and 35 USC 103 are provided. With this Amendment, it is believed that all claims are in condition for immediate allowance. Notice of Allowance is respectfully requested.

The Commissioner is authorized to charge or credit Deposit Account No. 16-1331 as needed for filing this response.

Respectfully submitted,

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